New cancer therapy may fight cardiovascular disease

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New drugs that are helping fight a multi-front war on cancer may do the same for cardiovascular disease, Medical College of Georgia researchers said.

Cancer and cardiovascular disease, both among top U.S. killers, share inflammation as a cause. Heat shock protein 90 inhibitors as a treatment could become additional common ground, said Dr. John Catravas, director of MCG's Vascular Biology Center.

"I think hsp90 inhibitors may be some of the best anti-inflammatory drugs we have," said Catravas, who is among the first scientists to explore the new cancer treatment's potential in cardiovascular disease.

Inflammation in the short term helps fight infection but becomes problematic when it is chronic or severe. For example, if acute inflammation causes contraction of endothelial cells (tight-fitting cells lining blood vessel walls), blood and fluid can leak into tissue - a particularly deadly scenario in the lungs where it causes acute respiratory distress syndrome.

"Fifty percent of patients diagnosed with acute respiratory distress syndrome die because their endothelial cells have been so damaged." Catravas said. He and his colleagues have shown that hsp90 inhibitors can block this cell contraction and subsequent swelling in laboratory mice with acute inflammation.

A new $1.8 million, five-year grant from the National Heart, Lung and Blood Institute will enable the team to also study hsp90 inhibitors' impact on the cardiovascular complications that typically occur in people with the common double whammy of type 2 diabetes and obesity.

Complications arise when chronic inflammation causes proliferation of smooth muscle cells inside blood vessel walls, prompting previously smooth and flexible walls to thicken and stiffen. "Our hypothesis is that if we treat them with hsp90 inhibitors, we should be able to reduce the cardiovascular problems associated with type 2 diabetes," Catravas said.

Hsp90 activates other proteins and keeps them on task - a multi-faceted role that leads the researchers to suspect that its inflammation-promoting role is multi-faceted as well. The functions are closely interwoven: enzymes critical to inflammation also activate hsp90.

Despite their critical role in the body, blocking hsp90 in disease states doesn't seem to cause undue problems. "Not all proteins associated with inflammation are bad, and when you block the good ones, you may have side effects," Catravas said. "But cancer indicates that the inhibitors have much higher affinity for active hsp90 and cancer has higher concentrations of active hsp90 than normal tissue." Catravas' team has shown that inflamed tissue has significantly more active hsp90 as well. "That is one of the beauties of the hsp90 inhibitors, he said.

They are focusing on three ways the inhibitors could block inflammation in cardiovascular disease. One is by blocking NFκB, which promotes synthesis of inflammation-promoting proteins. "We want to show if one of the ways it blocks especially chronic inflammation, which is NFκB-dependent, is by preventing NFκB activation," he said.

They'll inhibit NFκB then see if hsp90 inhibitors are still active and measure NFκB activity in mice treated with hsp90 inhibitors. They also

want to delineate how inhibitors block NFκB, to see if they can find an even better way than hsp90 inhibitors to block inflammation. They'll also further test their hypothesis that inhibitors selectively target hsp90 in inflamed, rather than normal, tissue.

Anti-inflammatory agents already in wide use likely aren't good options for inflammation-related cardiovascular disease, Catravas said, noting unacceptable side effects particularly with long-term use. He hopes hsp90 inhibitors will provide a less toxic, multi-target approach for some patients, he said. "This is the beginning of the field."

Provided by Medical College of Georgia